(b) transfecting a vector expressing the repressor.

REMARKS

Applicants respectfully request favorable reconsideration in view of the herewith presented amendment and remarks.

Claims 1-7, 9-17, and 19-37 are pending. Claims 1-7, 9-17, and 19-37 stand rejected. Please cancel claim 20 and withdraw it from consideration without prejudice as being directed to non-elected inventions. Please cancel claims 21-37 without prejudice.

No new matter has been introduced by the amendments made to the specification. The amendment made to the description of the specification simply corrects a typographical error.

The amendment to claim 1 corresponds to the Examiner's suggestions in the Official Action dated March 27, 2002 (see page 9). The changes to claim 1 are requested in order to place claim 1 in better form. Support for these amendments is found at page 16, lines10-20. Further, the amendment to step (a) of claim 1, where the repressor binding site is located between, within, or surrounding the adenovirus packaging sequence, is supported throughout the specification, for example, at page 5, line 30, to page 6, line 7.

The amendment of step (b) of claim 1 is supported in the specification, for example, at page 17, lines 22-25; at page 20, lines 28-35; and at page 10, line s 24-34. Further, support for the Examiner's suggested recitation "a promoter operatively linked to the heterologous gene", (see page 6, lines 9-10, of the Official Action dated March 27, 2002), is found at page 17, line 25, to page 18, line 5. Lastly, support for the recitation "a second adenovirus packaging sequence" is found at page 17, lines 4-7.

Support for the amendments made to step (c) of claim 1 is found throughout the specification, for example, at page 18, line 26, to page 19, line 11, where propagating the helper adenovirus vector of step (a) and the DNA delivery adenovirus vector of step (b) occurs in a cell-line. Support for the amendments made to step (d), which involve repressing packaging of the helper adenovirus vector, is found throughout the specification, for example, in the paragraph beginning at page 19, line 17.

The amendments to claims 4 and 5, where the propagation step occurs in a first cell-line and then virus particles are transferred to a second cell-line for repression, are supported in the specification, for example, at page 6, lines 29-35.

No new matter has been introduced by the claim amendments. Applicants respectfully request entry and consideration of the amendments.

35 USC §101

Claim 21 and dependent claims therefrom have been rejected under 35 USC §101 because the Examiner contends that these claims are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. Specifically, the Examiner argues that "the disclosed use of the adenovirus vector is for delivering a nucleic acid to a cell and not packaging a helper adenovirus vector" (Paper No. 14, pg. 4). Applicants respectfully disagree with this rejection.

As an initial matter, applicants assert that the instant invention is directed towards a viral vector delivery system and specifically, a method of regulating adenovirus packaging. In particular, the Examiner's attention is respectfully directed to pages 4-5 of the instant specification where objects of the invention are described. The objects are directed to adenovirus vectors, regulation of viral particle production through the packaging signal, and the use of such regulated adenovirus vectors in a DNA delivery system.

As the Examiner is well aware, an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. §101 and 35 U.S.C. §112. Further, "When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. §101 is clearly shown" (See, e.g., *Raytheon v. Roper*, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984)). Applicants direct the Examiner's attention to the Background section of the instant specification which describes the various advantages of using the adenovirus and adenovirus-based vectors as a human DNA delivery system (pgs. 1-4). Specifically, in order to transfer a nucleic acid to a cell, it must first be properly packed into the adenovirus. For example, the instant specification states "Adenovirus DNA encapsidation occurs in a polar manner from left to right and relies on a cis-acting packaging domain located

between approximately nt 200-380 (Daniell et al. (1976); Hammerskjoeld et al. (1980); Hearing et al. (1987); Robbinson et al. (1984); Tibbetts (1977))" (pg. 2, lns. 25-31). Furthermore,

> A major goal in DNA delivery systems is to create a viral vector that lacks all viral coding sequences, and only contains DNA of interest for delivery purposes plus minimal viral DNA sequences required for growth and production of the virus. To grow such a virus, a helper virus is required, but selection against contamination of the virus stock with the helper virus (wild type virus) must be imposed. (pg. 3, lns. 17-25)

The instant specification describes the various embodiments of constructing suitable vectors for delivery nucleic acids. As the Examiner has cited on page 16, lines 20-24, "The vectors of the present invention are useful in DNA delivery systems to help curb the production of replication competent adenovirus (RCA), a virus that is dangerous and potentially toxic to a patient receiving it during patient administration." Applicants assert that one skilled in the art would recognize the utility of adenovirus as a nucleic acid delivery system, and further understand that the packaging of nucleic acids in the adenovirus is necessary for delivery into cells. No further research is necessary and a "real world" use is described. Applicants respectfully traverse the Examiner's grounds of rejection; however, in order to expedite prosecution of the instant application, claims 21-25 have been cancelled rendering this §101 rejection moot.

35 USC §112, First Paragraph

Claim 21 and dependent claims therefrom have been rejected under 35 USC §112, first paragraph, because the Examiner states claim 21 is not supported by either a substantial and specific asserted utility or a well established utility, and one skilled in the art would not know how to use the claimed invention. Applicants respectfully disagree with this rejection.

As an initial matter, applicants respectfully direct the Examiner's attention to pages 17-19 of the previous response to Office Action dated March 27, 2002. Applicants provided support for additional claims 21-37 and amendments made to pending claims 1-7, 9-17, and 19. Applicants respectfully disagree with this rejection. However, in order to expedite prosecution of this application, claims 21-25 have been cancelled rendering this §112, first paragraph rejection moot.

Claims 1-7, 9-17,19, 21-37 have been rejected under 35 U.S.C. §112, first paragraph as the Examiner contends the specification does not provide enablement for the full scope of the claimed invention. Applicants respectfully disagree with the Examiner's ground for rejection.

The Examiner contends that the specification as originally filed "only contemplates producing replication defective adenoviruses and lacks sufficient guidance for one skilled in the art to make replication competent adenoviruses" (Paper No. 14, pg. 10). Applicants assert that the DNA delivery adenovirus alone cannot replicate and is replication defective. The helper adenovirus once repressed, is also replication defective. Applicants point out that the DNA delivery adenovirus and helper adenovirus vectors have different packaging sequences, i.e., A repeats and opposite DNA orientation, thereby greatly minimizing homologous recombination. Throughout the instant specification as well as Examples, sufficient guidance and enablement is provided for one skilled in the art to make and use the claimed invention. Applicants have cancelled claims 21-37 without prejudice rendering the §112, first paragraph rejection to these claims moot. Reconsideration and withdrawal is respectively requested for this §112, first paragraph rejection.

The Examiner further contends that claims 4 and 5 lack essential steps for how the recombinant viruses from the propagating step are removed from the first cell-line and placed into the second cell-line. Applicants respectfully traverse the Examiner's contention. The method of claim 5 does not include a second cell-line. In fact, the same cell-line used in propagating step (c) of claim 5 is also used in the repressing step (d). Thus, claim 5 is complete and does not omit any essential steps.

The Examiner rejects claim 4 for lack of enablement, yet applicants emphasize that the adenovirus vector, its novel elements and a method of using such a vector are described in detail in the instant specification. Factors such as the technique of transfecting cells and extracting viral DNA, selection of genes of interest, dosage and viral particle load aspects of the invention within the skill in the art. As stated in *In re Goodman*, 29 USPQ.2d at 2013 (Fed. Cir. 1994) "It is the specification, not the knowledge of one skilled in the art, that must supply the novel

aspects of the invention in order to constitute adequate enablement." Applicants contend that the "novel aspects" of the invention are described and claimed.

Furthermore, the Examiner's attention is respectfully directed to page 19, lines 5-11 and page 28, lines 1-8, which describes viral growth in one cell-line and the transfer of virus into another cell-line, and the Hirt procedure (Hirt, B. 1967. J. Molec. Biol. 26: 365-369) for analysis of viral DNA obtained from infected 293 cells. Also cited in the application is a reference article by Schmid and Hearing (J. Virol. 72(8):6339-6347, 1998) which describes how the skilled artisan would infect and obtain viral DNA. Both the Hirt reference and Schmid and Hearing reference are incorporated by reference in the instant specification (pg. 28, ln. 6; pg. 40, ln. 29). Applicants assert that one skilled in the art would understand the commonly known techniques for obtaining virus from the first cell-line and transferring virus particles from one cell-line to another in order to infect the second cell-line. Not only does the instant specification provide the Hirt and Schmid references as a guide for such a technique, but the knowledge in the art at the time of filing was sufficient for enabling one skilled in the art to isolate the propagated viruses and transfer the viruses into another cell-line for repression. Applicants, however, have amended claim 4 to more clearly indicate that virus particles produced in the first cell-line are transferred to infect a second cell-line. Reconsideration and withdrawal of this §112, first paragraph rejection is respectfully requested.

Claims 9 and 19, directed to a method of administering a replicant defective adenovirus to a mammal, have been rejected to under 35 U.S.C. §112, first paragraph for lack of guidance and enablement. Applicants respectfully traverse this ground for rejection.

The Examiner specifically points to Anderson (1998) and Verma (1997) which report several factors for consideration in gene transfer and DNA therapy protocols. Applicants assert that the art provides sufficient guidance and parameters such that one skilled in the art would be able to understand the invention as described by the instant specification.

Applicants respectfully direct the Examiner's attention to a review by Ron Crystal, where adenovirus vectors have been used for the treatment of tumors as observed in *in vivo* and *ex vivo* gene therapy (Crystal, R.G. Cancer Chemother. Pharmacol. 43(suppl):S90-S99, 1999). The

review describes adenovirus vectors for enhancing local control of and systemic immunity against cancer. In particular, the adenovirus vector of Crystal was used to "deliver to the tumor a gene encoding an enzyme that converts an innocuous prodrug to an active chemotherapeutic agent in the local milieu" (page S91, left column, lines 12-15). Also, Crystal describes the use of adenovirus vectors for the delivery of a gene encoding a tumor antigen specifically to modify dendritic cells, thereby stimulating immunity against the tumor (page S91, left column, lines 23-28). The art provides guidance on how to deliver genes using viruses, such as adenoviruses. One skilled in the art would be knowledgeable of the genes and parameters necessary for therapeutic gene expression as described in the art. The instant invention provides a model system using vectors for delivering such genes for the prevention or treatment of the specific gene-associated diseases. Therefore, the art, as further described below, has substantial information providing guidance and parameters with which one skilled in the art would be able to understand the present invention as is described in the specification.

The Examiner points to deficiencies in gene therapy, such as poor delivery systems, both viral and non-viral, and poor gene expression after delivery as taught by Anderson (pp. 25-30). However, Verma presents the positive aspects of gene therapy and describes the evolution of adenovirus vectors, *i.e.*, first generation to 'gut-less' to overcome problems related to immune response. Verma also lists the various benefits of using adenoviruses as a means for delivering DNA, where adenovirus vectors can accommodate large inserts, adenoviruses may be grown to high concentrations and infect both dividing and non-dividing cells. Although triggering an immune response may be problematic, 'gut-less' adenovirus vectors have been constructed to address this problem. Furthermore, on page 242, col. 3, Verma states that "the promises are still great, and the problems have been identified (and they are surmountable)" (emphasis added). Therefore, applicants assert that the art provides sufficient guidance and together with the instant specification enables one skilled in the art to use the invention for delivering DNA.

Applicants assert that the instant invention is directed towards a viral vector delivery system and not to a method for treating a specific disease. In particular, the Examiner's attention is respectfully directed to pages 4-5 of the instant specification where objects of the invention are described. The objects are directed to adenovirus vectors, regulation of viral particle production

through the packaging signal, and the use of such regulated adenovirus vectors in a DNA delivery system. The instant specification simply provides diseases suitable for gene therapy that include, but are not limited to, those diseases that may be treated with genes encoding IL-2, p53, alpha1-antitrypsin, CFTR, and clotting factor. The adenovirus delivery system is such that any gene may be used for delivery. Therefore, the skilled artisan would recognize examples of known diseases and their genes for use in the present invention, as defined in the instant specification. The instant specification with the parameters known in the art provide sufficient guidance for the skilled artisan to construct the claimed adenovirus vector to delivery the desired gene. Examples of every possible embodiment of the invention need not be expressly set forth.

The Examiner specifically points to the Vile reference as teaching the state of the art at the time the application was filed and for cancer gene therapy. The Examiner contends that the concerns regarding problems of cancer gene therapy in general would not enable the claimed adenoviral vector for any route of administration other than intra-tumoral administration. Applicants respectfully disagree.

Specifically, the Examiner's attention is directed to page 3 of the Vile reference ("Vector" section) where

> the situation where tumour/immune cells are manipulated *ex vivo*, there will be a clear preference in the coming years for the use of adenoviral vectors for *in vivo* delivery to tumours. Dominant in the selection process is the high titre of adenoviruses (>10^{11} p.f.u./ml) compared with other vectors. Given the requirement to kill, rather than correct, target cells, there is generally little need for integration (i.e. long-term gene expression as provided by C-type and lentiviral vectors). The initial rationale of the use of the C-type retroviral vectors to target exclusively dividing tumour cells on the background of a quiescent tissue is being gradually superseded by the realisation that human tumours generally cycle much more slowly than the rodent cell lines on which this strategy was based. Hence, the trade-off between the total numbers of cells that can be productively infected by an adenovirus, compared with the loss of a potential targeting advantage using C-type retroviruses, clearly favours the more efficient adenoviral system. In addition, the immunogenicity associated with the loss of adenoviral vectors probably offers an added 'adjuvant' bonus in the context of most cancer protocols. As a result, the number of

> direct in vivo delivery protocols will continue the escalation of the use of adenoviruses. (emphasis added)

Vile describes cancer gene therapy using adenoviruses which may not target tumor cells but more efficiently produces adenoviruses with the gene of interest. Since Vile suggests that the infectivity of adenoviruses overcomes the loss of targeting, the claimed adenoviral vector is enabled for treating a tumor by a means other than intra-tumoral administration. Therefore, applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

The Examiner uses Albelda as a reference describing α1-antitrypsin gene therapy. The section quoted by the Examiner simply provides a general overview of gene therapy and not specific for the use of adenoviral vectors as a DNA delivery system. Applicants respectfully direct the Examiner's attention to page 651, col. 2, section "α1-Antitrypsin Deficiency" of the Albelda reference. Specifically, the article states that "two potentially promising developments in this area are a new • 1-antitrypsin-encoding adenoviral vector in which all viral coding sequences have been deleted and an adeno-associated virus vector encoding α1-antitrypsin that can be injected intrahepatically." Additionally, the use of adenovirus vectors with deleted E1 and E3 regions of the virus and containing the CFTR transgene showed promise as indicated in Table 2 (Knowles, et al. and Bellon, et al.). Table 2 provides guidance in dosage, administration, and vector type where use of the adenovirus resulted in low to modest immune response and toxicity. Therefore, the Albelda reference provides sufficient guidance, with the description provided by the instant specification, for the skilled artisan to construct and use the claimed adenovirus DNA delivery system.

Furthermore, the Examiner points to Bigger as describing major obstacles for lung gene therapy. However, applicants point to Bigger, (page 627, col. 2, 3rd par.) where guidance is provided as to virus levels for infecting those affected by CF and delivery methods. The Examiner specifically points to Bigger (page 638, col. 2, 1st par.) which describes thick mucus in the airway of CF patients creating a problem of gene delivery to the lung. However, Bigger further describes methods of alleviating this problem, i.e., by using human recombinant DNase prior to transfection with gene therapy vectors or using an antibiotic inhalation pretreatment in

order to decrease the inflammation in the airways. Use of these methods in conjunction with the adenoviral vector delivery system provide sufficient guidance for one skilled in the art to overcome the obstacles for lung gene therapy. Therefore, applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

Regarding Factor VIII gene therapy, the Examiner uses Hortelano to demonstrate that there are problems of achieving high and sustained levels of factor delivery and issues related to efficacy. Applicants note, however, that Hortelano also describes the advantages of using adenoviruses and means for overcoming or reducing detrimental immunogenicity (page 9, lns. 4-30). In particular, Hortelano even reports that

> vectors devoid of all viral sequences have been generated in an attempt to eliminate the cause of the immune response to adenoviral vectors, thus allowing the long-term delivery of the transgene product. The use of optimized adenovirus vectors has allowed for persistent physiological levels of hFVIII in hemophilia mice for at least 9 months. Such encouraging finding[s] may open the possibility to initiate human trials in the near future. (emphasis added)

Therefore, the Hortelano reference, teachings in the art, as well as the instant specification provide sufficient guidance as to how the skilled artisan would construct and use recombinant adenovirus vectors for Factor VIII gene therapy.

An invention need not solve ALL of the problems in the art in order to be new and patentable. The present invention specifically addresses the problem of replication competent adenoviruses. This problem stems from two viruses which may recombine to generate a replication competent adenovirus. The present invention solves this problem by having different adenovirus packaging sequences that are regulated so that the production of viral particles is controllable. Since the helper adenovirus vector has repressor binding sites located between, within, or surrounding its adenovirus packaging sequence, and the adenovirus packaging sequences of the helper and the DNA delivery adenovirus vectors are different and have different DNA orientations, a target for homologous recombination does not exist in the packaging domain, thereby minimizing the possibility of recombination between the two viruses. The present novel DNA delivery system using adenovirus vectors having different and controllable

packaging sequences is described in detail in the instant specification, as is its effectiveness for its intended purpose. No more is required by the statute.

Applicants assert that there is sufficient guidance in the art for teaching how one skilled in the art would, without undue experimentation, make and use the adenovirus delivery system. The various references cited herein together with the description in the instant specification, enable the skilled artisan as to how to make and use the adenoviral vector as claimed. Applicants further assert that the art provides a reasonable degree of success in adenovirus DNA delivery. Therefore, reconsideration and withdrawal of this §112, first paragraph rejection is respectfully requested.

35 USC §112, Second Paragraph

The Examiner has rejected claims 1, 21, and claims dependent therefrom under 35 U.S.C. §112, second paragraph because these claims do not particularly point out the order of steps listed in each claim. Although the grounds for rejection are traversed, applicants have amended claim 1 by pointing out the order of the steps listed in the claim in order to address the Examiner's concerns. Claims 21-25 have been cancelled without prejudice. Therefore, reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

Claims 1, 21, and claims dependent therefrom are rejected under 35 U.S.C. §112, second paragraph as being incomplete for omitting steps. Applicants respectfully disagree; however, in order to expedite prosecution of this application, applicants have amended claim 1 and cancelled claims 21-25 without prejudice. Specifically, step (d) of claim 1 has been amended to more clearly indicate how the repressing step occurs, *i.e.*, by binding a repressor to the repressor binding site, thereby repressing packaging of the adenovirus vector. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

The Examiner has rejected claims 4 and 5 under 35 U.S.C. §112, second paragraph for omitting essential steps, thereby amounting to a gap between the steps. Applicants respectfully traverse this ground for rejection.

As previously described under 35 U.S.C. §112, first paragraph, claim 5 does not omit any essential steps as this claim simply refers to a method using one cell-line. Applicants assert that the specification need not be burdened with information available in the prior art. In fact, what is well-known is best omitted. In *re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

As previously mentioned in 35 U.S.C. §112, first paragraph, the claim does not omit any essential steps, nor is there a lack of enablement. Applicants respectfully remind the Examiner that only the "novel aspects" of the invention need be claimed. The Examiner's attention is respectfully directed to the Hirt procedure (Hirt, B. J. Molec. Biol. 26:365-369, 1967) and Schmid reference (J. Virol. 72(8):6339-6347,1998), as incorporated by reference in the instant specification, which describe how one would remove virus from infected cell cultures and transfer the virus to infect another cell-line. Applicants assert that the skilled artisan would be knowledgeable as to these steps from the art and from the description provided in the instant specification and that claim 4 does not omit any steps necessary for the skilled artisan to perform the claimed invention. However as previously mentioned, in order to address the Examiner's concerns, claim 4 has been amended to more clearly indicate that virus particles produced in the first cell-line are transferred to infect a second cell-line. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

CONCLUSION

As required by 37 C.F.R. §1.121, "marked up" versions of the amended claims and of the replacement paragraphs of the specification are attached herewith with additions indicated by underlining and deletions by brackets.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 3927-4133US2.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 3842-4050. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted

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Dated: March 3, 2003

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APPENDIX

(Additions are indicated by underlined text and deletions are indicated by [bracketed text].

IN THE SPECIFICATION

Please amend the specification as follows:

The paragraph on page 5, lines 10-29, has been amended as follows:

The present invention relates to adenovirus vectors containing a minimum packaging signal for producing adenovirus virions. Of special importance is the presence of a CG dinucleotide located downstream of a TTTG sequence within each of the packaging elements. Spacing between the consensus segment 5'-TTTG-3' and the 5'-CG-3' segment located downstream is preferably between 1 and 12 nucleotides. Alternatively, it [amy]may be preferred to configure the consensus segments so that these elements appear on the same surface of the DNA helix. Most preferably, the adenovirus vector of the present invention may contain a packaging element consisting of 5'-TTTGN_8CG-3' (SEQ ID NO:1) which represents a minimal sequence necessary for adenovirus packaging. This sequence is preferably present in multiple copies. One type of minimal packaging sequence is an "A repeat", which contains a consensus sequence. Several A repeat sequences are shown in Table 1.

IN THE CLAIMS

Please amend the claims as follows:

1. (Third amendment) A method of regulating adenovirus packaging comprising the steps of:

(a) obtaining a helper adenovirus vector containing a first adenovirus packaging sequence comprising a repressor binding site, wherein the repressor binding site is located between, within, or surrounding the adenovirus packaging sequence;

(b) obtaining a DNA delivery adenovirus vector comprising 5' and 3' inverted terminal repeats; a second adenovirus packaging sequence; a heterologous gene; and a promoter operatively linked to the heterologous gene;

(c) propagating the helper adenovirus vector of (a) and the DNA delivery adenovirus vector of (b) in a cell-line; and

(d) repressing packaging of the helper adenovirus vector of (c) by binding a repressor [which binds] to the repressor binding site contained in the helper adenovirus vector.

4. (Third amendment) The method according to claim 1, wherein the propagating step for the helper adenovirus occurs in a first cell-line thereby forming virus particles containing the helper adenovirus vector, transferring the virus particles to a second cell-line, and the repressing step occurs in [a]the second cell-line, wherein the repressing step [in the second cell-line] further comprises a step selected from the group of steps consisting of:

(a) endogenously expressing the repressor; and

(b) transfecting a vector expressing the repressor.